Structural Basis for Discrimination of 3-phosphoinositides by Pleckstrin Homology Domains

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Abstract No. Ferg9010
Beamline(s): **X25, X12B**

Introduction: Pleckstrin homology (PH) domains are protein modules of around 120 amino acids found in many proteins involved in cellular signaling. Certain PH domains drive signal-dependent membrane recruitment of their host proteins by binding strongly and specifically to lipid second messengers produced by agonist-stimulated phosphoinositide 3-kinases (PI 3-K's). Some PH domains (e.g. from Grp1) are specific for PtdIns(3,4,5)P_3, while others (e.g. from DAPP1) binds strongly to both PtdIns(3,4,5)P_3 and its 5'-dephosphorylation product, PtdIns(3,4)P_2. Since the different PI 3-K products have distinct roles in cellular signaling, it is important to know which PH domains will recognize which phosphoinositides.

Methods and Materials: Four X-ray crystal structures were solved of two different PH domains; unliganded DAPP1-PH (by MIR, to 2.4 Å), DAPP1-PH/Ins(1,3,4,5)P_4 complex (by MR, to 1.8 Å), Grp1-PH/Ins(1,3,4,5,6)P_5 complex (by MIRAS, to 1.9 Å) and Grp1-PH/Ins(1,3,4,5)P_4 complex (by MR plus AS, to 2.5 Å).

Results: Both PH domains share a set of core interactions with the 1-, 3- and 4-phosphates of Ins(1,3,4,5)P_4. This common set of interactions appears insufficient to confer high affinity binding. Additional, distinct interactions define the phosphoinositide specificity of each PH domain. For DAPP1, these are made to the 4-phosphate, while the additional interactions focus on the 5-phosphate of Ins(1,3,4,5)P_4 in the complex with Grp1-PH domain.

Conclusions: Comparison of the two structures provides an explanation for the distinct phosphoinositide specificities of the two PH domains, and allows us to predict the 3-phosphoinositide selectivity of uncharacterized PH domains.

Acknowledgments: These projects were supported by the NIH (NIGMS grant GM56846 to M.L.), the U.S. Army Breast Cancer Research Program (DAMD17-98-1-8228 to K.F.), and a Damon Runyon Scholar Award from the Cancer Research Fund of the Damon Runyon-Walter Winchell Foundation (to M.L.).

References: K.M. Ferguson, J.M. Kavran, V.G. Sankaran, E. Fournier, S.J. Isakoff, E.Y. Skolnik, and M.A. Lemmon, "Structural Basis for Discrimination of 3-phosphoinositides by Pleckstrin Homology Domains," Molecular Cell, **6**, *373*, 2000.

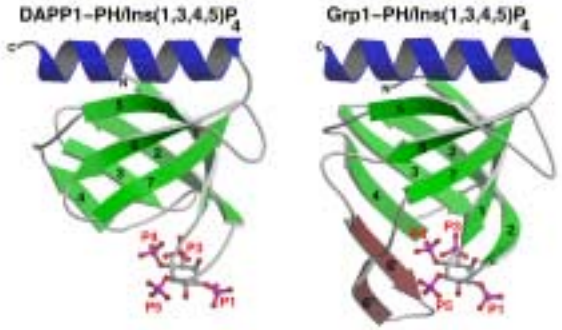

Figure 1. Ribbon representations of the DAPP1-PH and Grp1-PH structures. The C-terminal amphipathic α-helix, common to all PH domains, is colored blue. β strands that form the core β sandwich of the PH domains are colored green and are labeled 1 through 7. The phosphate positions in the bound inositol phosphates are numbered in red.